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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/493,353	01/28/00	LINNEN J	CDS-211

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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev.11/00)

Office Action Summary	Application No. 09/493,353	Applicant(s) LINNEN ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 15 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 12 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 17, 2001. Currently, claims 1-64 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

Priority

3. This application claims priority to 60/118,497, filed February 3, 1999.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-13, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991).

Han et al. (herein referred to as Han) teaches the sequence of 341 base pairs from the 5' untranslated region (UTR) of HCV and alignment of this sequence from several different HCV isolates. Han teaches extracting the plasma from HCV-positive or negative blood donors. RNA was isolated and converted into single-stranded cDNA by

reverse trancriptase using the appropriate cDNA primer (pg 1711, col 2). Han teaches primers for the PCR amplification of 5' UTR and means of cloning these PCR products (pg. 1711, col. 2, and Figure 2). The PCR products were analyzed by southern blot hybridization using a labeled oligonucleotide probe (pg 1711, col 2). Han teaches that when the sequence of the 5' UTR is compared among isolates, there is a high degree of sequence homology and that the sequence mismatches that are present are clustered in 5 positions, as taught in Figure 2 (see also pg. 1713, para 1). Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4). Han teaches Primer 51 was used to primer cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a. Primer 95 overlaps SEQ ID NO: 1, CAGAAAGCGTCTAG are in common.

Han does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill

would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 5' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Han to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Han. Since Han provides an alignment of several isolates which show conserved regions between the isolates, and delineates the ORFs, the ordinary artisan would have been motivated to have designed primers which amplify various regions of interest from the 5' UTR region. Specifically, the skilled artisan would have picked SEQ ID NO: 1 and 4 to have amplified the ORF2 and would have chosen SEQ ID NO: 2 and 7, SEQ ID NO: 3 and 5 or SEQ ID NO: 3 and 6 which flank ORF3. Furthermore, the skilled artisan would have chosen SEQ ID NO: 11, 12 or 13 for probing the detection of HCV. The ordinary artisan would have been motivated to amplify the 5' UTR region of HCV since Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose. Thus, any primers which amplify the 5' UTR region and any probes within the 5' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The rejection is not applicable to the primer pair of SEQ ID NO: 1 and 4 and the primer pair of SEQ ID NO: 2 and 7, since the specification provides unexpected results with respect to these primer pairs.

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. Applicants cite *In re Deuel, In re O'Farrell* and states that there is no reasonable expectation of success.

Applicant's cite a passage, in addition to the passage provided, in *Deuel* which is deemed to support applicant's position. The examiner agrees with the position that the Deuel court states "in all of these cases...the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention". However, the examiner also notes that Deuel teaches at 1215, col. 1, No. 7, "Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules". In contrast, in the instant case, the very source of the claimed nucleic acid was provided. The reference even directs the attention to the very region the oligonucleotides are pulled from. Deuel did not find it obvious to probe a library to find full length DNA

molecules given a smaller portion of the molecule. The instant case, however, is directed to a known full length molecule and determining smaller molecules which may function as probes and/or primers. Thus, the normal circumstances for a prima facie case should be followed as set out on 1214, col. 2. Han has taught four primers which amplify 5' UTR and two probes for this region. Han teaches Primer 51 was used to prime cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). SEQ ID NO: 12 overlaps primer 51. Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a. Primer 95 overlaps SEQ ID NO: 1, i.e., the sequence CAGAAAGCGTCTAG is in common.

Applicant then argues that there is no reasonable expectation of success. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art to select primers which hybridize to the 5' UTR of HCV for detection of the nucleic acid. Further, since the art teaches the SEQ ID NO: 3, 5-7, 13-14, 16 and a nucleic acid comprising SEQ ID NO: 4, the art has provided specific motivation and teachings to choose the probes and primers for the HIV-1 and HIV-2 detection. These probes and primers were used in a multiplex analysis of HIV-1 and HIV-2 detection, thus there is motivation to select these sequences for multiplex analysis. With respect to choosing primers for 5' HCV detection, the prior art disclosed numerous different

primer sequences and teaches selection of primers or probes which detect the HCV 5' UTR. The prior art teaches the parameters (i.e. size, parameters, homology) necessary to vary to achieve specific probes, and the prior art successfully meets this test. This is sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that, "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. For the 5' UTR primers, this is not a situation where the prior art fails to identify critical parameters since the prior art provides the parameters necessary for primer selection, including preferred sequence regions (see Figure 2 of Han et al,), the entire sequence at issue (see Figure 2 of Han), and a variety of particular functional species. Therefore, the prior art provides the information necessary to select probes and primers and the prior art would expect that every species selected in this manner would function in a detection assay. This is also not a situation where only general guidance was given. The prior art provides specific guidance regarding the use of primers and probes from this region of the HCV genome for detection purposes. Therefore, properly applying O'Farrell, it is not simply obvious to try to make the claimed invention, there is a reasonable expectation of success.

The applicant's further argue there is not any such reasonable expectation of success. Applicant's argument directed to there is no reasonable expectation of success is apparently supported by Ausubel. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection. For example, computer programs exist which allow user input for primer selection parameters (see Nucleic Acids Research, 1994). The response asserts that the computers are also not foolproof, however, foolproof is not the standard to be met. As stated in O'Farrell, "obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law non-obvious". Thus, absolute predictability is not required. The art provides the full length sequence of the

5'UTR of HCV, the regions of interest and the approximate size of oligonucleotides to select from this region for detection of the region. Further, optimization of primers and primer pairs is routine in the art. The art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

The examiner also notes that some of the claims for detecting the nucleic acid are not merely drawn to the specific probe oligonucleotides, the claims use open language, namely comprising to describe the probes, i.e. Claim 13.

5. Claims 43, 45, 47, 49-50, 54, 56, 58, 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) as applied to Claim 1, 3-13, 40-42 above, and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Han does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Han with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Han into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Han's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers taught by Han included, into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

6. Claims 14, 16-26, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996).

Kolykhalov et al. (herein referred to as Kolykhalov) teaches a highly conserved sequence at the 3' terminus of the HCV genome RNA. Kolykhalov teaches preparing

HCV RNA from human serum (pg 3363, col 2)(limitations of Claim 21). Kolykhalov teaches using nested primer pairs corresponding to a region in the 5'NTR for RNA isolation (pg 3363, col 2). Furthermore, Kolykhalov teaches using primer pairs specific for the novel 98-base element at the 3' end of the HCV genome to analyze for the presence of novel sequences (pg 3364, col 1)(limitations of claim 16). PCR products were analyzed by electrophoresis on a polyacrylamide gel (limitations of Claim 14, 17, 18). Kolykhalov teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. The region is also found at the 3' termini of several independent HCV isolates which is highly conserved with between 98-100% sequence identity for the examined isolates. Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy"(pg 3370, col 2).

Kolykhalov does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill

would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 3' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Kolykhalov to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 3' UTR region to detect HCV, as taught by Kolykhalov. Since Kolykhalov provides an alignment of several isolates which show conserved regions between the isolates (Figure 3), the ordinary artisan would have been motivated to have designed primers which amplify the 98-nucleotide conserved region from the 3' UTR region. Specifically, the skilled artisan would have picked primers from the 5' and the 3' end of the 98-nucleotide conserved region of the 3' UTR which were conserved among the isolates, for example SEQ ID NO: 8 and SEQ ID NO: 9. Furthermore, the skilled artisan would have probed the sequence with a probe such as SEQ ID NO: 14 or 15 which would detect the specific isolates desired. The ordinary artisan would have been motivated to amplify the 3' UTR region of HCV since Kolykhalov teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. Additionally, Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for

HCV diagnosis and therapy". Thus, any primers which amplify the 98-nucleotide conserved region of the 3' UTR region and any probes within this 3' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. Applicants cite *In re Deuel, In re O'Farrell* and states that there is no reasonable expectation of success.

Applicant's cite a passage, in addition to the passage provided, in *Deuel* which is deemed to support applicant's position. The examiner agrees with the position that the Deuel court states "in all of these cases...the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention". However, the examiner also notes that Deuel teaches at 1215, col. 1, No. 7, "Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules". In contrast, in the instant case, the very source of the claimed nucleic acid was provided. The reference even directs the attention to the very region the oligonucleotides are pulled from. Deuel did not find it obvious to probe a library to find full length DNA

molecules given a smaller portion of the molecule. The instant case, however, is directed to a known full length molecule and determining smaller molecules which may function as probes and/or primers. Thus, the normal circumstances for a prima facie case should be followed as set out on 1214, col. 2. Kolykhalov specifically teaches oligonucleotide 284 which encompasses SEQ ID NO: 2 and 3. SEQ ID NO: 2 and 3 are embedded within the oligonucleotide of 284. SEQ ID NO: 4, 5, 6 and 1 extend one, two, three and four nucleotides beyond the oligonucleotide of 284, however these sequences are within the same region of conserved nucleotides as taught by Kolykhalov. The ordinary artisan would have been motivated to have targeted this region as specifically identified by Kolykhalov.

Applicant then argues that there is no reasonable expectation of success. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art to select primers which hybridize to the 3' UTR of HCV. The prior art disclosed numerous different primer sequences and teaches selection of primers or probes which differentially detect the HCV 3' UTR. The prior art teaches the parameters necessary to vary to achieve specific probes, and the prior art successfully meets this test. This is sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that, In some cases,

what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art fails to identify critical parameters since the prior art provides the parameters necessary for primer selection, including preferred sequence regions (see Figure 3 of Kolykhalov et al), homology considerations (page 3363), the entire sequence at issue (Figure 3), and a variety of particular functional species. In the instant case, however, the art teaches explicitly points to specific regions of interest, namely oligonucleotide 284 which is within a conserved region between the clones of HCV. The oligonucleotides of Kolykhalov are approximately the same length. Therefore, the prior art provides the information necessary to select probes and primers and the prior art would expect that every species selected in this manner would function in a differential detection assay. This is also not a situation where only general guidance was given. The prior art provides specific guidance regarding the use of primers and probes from this region of the HCV genome for detection purposes. Therefore, properly applying O'Farrell, it is not simply obvious to try to make the claimed invention, there is a reasonable expectation of success.

Finally, with respect to the "reasonable expectation of success", the applicants assert there is not any such reasonable expectation of success. Applicant's argument directed to there is no reasonable expectation of success is apparently supported by Ausubel. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection. For example, computer programs exist which allow user input for primer selection parameters (see Nucleic Acids Research, 1994). The response asserts that the computers are also not foolproof, however, foolproof is not the standard to be met. As stated in O'Farrell, "obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law non-obvious". Thus, absolute predictability is not

required. The art provides the full length sequence of the 3'UTR of HCV, the regions of interest and the approximate size of oligonucleotides to select from this region for detection of the region. Kolykhalov specifically teaches oligonucleotide 284 which encompasses SEQ ID NO: 2 and 3. SEQ ID NO: 2 and 3 are embedded within the oligonucleotide of 284. SEQ ID NO: 4, 5, 6 and 1 extend one, two, three and four nucleotides beyond the oligonucleotide of 284, however these sequences are within the same region of conserved nucleotides as taught by Kolykhalov. The ordinary artisan would have been motivated to have targeted this region as specifically identified by Kolykhalov. Further, this argument has been reviewed but is not convincing because optimization of primers and primer pairs is routine in the art. The art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 51-53 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) as applied to Claims 14, 16-26, 40-42 above, and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Kolykhalov does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Kolykhalov with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Kolykhalov into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Kolykhalov's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers included, into a kit for all of the reasons

of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 14, 16-26, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998).

Tanaka et al. (herein referred to as Tanaka) teaches the 3' UTR region of HCV. As seen in Table 2, numerous primers and a probe for this region are taught. Tanaka also teaches analysis of clinical samples (col 8). RNA was prepared from serum and reverse transcription was carried out using specific primers (col. 8, lines 18-22)(limitations of Claim 16, 17, 21). The cDNA synthesized was mixed with primers, and the PCR product was detected upon agarose electrophoresis (col 11, lines 10-16)(limitations of Claim 18, 24). A southern blot was also used for conformation (limitations of Claim 19, 25). A probe R3 was used for detection (col 11).

Additionally, Encke et al. (herein referred to as Encke) teaches "recently, a highly conserved, 98 nucleotide long sequence at the very 3' end of the HCV genome which is the third region has been described and appears to play an important role in viral replication and possible infectivity (pg 118, col 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Tanaka and the teachings of Encke to obtain the claimed invention as a whole. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the

existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 3' UTR of the HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. The skilled artisan would have been motivated to have used primers from the 3' UTR region to detect HCV, as taught by Tanaka, for the express benefit of detecting a "recently, a highly conserved, 98 nucleotide long sequence at the very 3' end of the HCV genome which is the third region has been described and appears to play an important role in viral replication and possible infectivity, as taught by Encke . Since Tanaka teaches the 3' UTR sequence and the 98 nucleotide conserved region, the skilled artisan would have designed primers within this 98 nucleotide region for the express benefit of detection of HCV. Thus, any primers which amplify the 3' UTR region would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify

HCV nucleic acids would have been obvious to one skilled in the art. Applicants cite *In re Deuel, In re O'Farrell* and states that there is no reasonable expectation of success.

Applicant's cite a passage, in addition to the passage provided, in *Deuel* which is deemed to support applicant's position. The examiner agrees with the position that the Deuel court states "in all of these cases...the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention". However, the examiner also notes that Deuel teaches at 1215, col. 1, No. 7, "Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules". In contrast, in the instant case, the very source of the claimed nucleic acid was provided. The reference even directs the attention to the very region the oligonucleotides are pulled from. Deuel did not find it obvious to probe a library to find full length DNA molecules given a smaller portion of the molecule. The instant case, however, is directed to a known full length molecule and determining smaller molecules which may function as probes and/or primers. Thus, the normal circumstances for a prima facie case should be followed as set out on 1214, col. 2. Tanaka teaches the full length 3'UTR region with specific probes and primers within the nucleic acid. Tanaka teaches that the 3'UTR sequence is highly conserved between clones and would be very useful

for the detection of HCV. As seen in Table 2, SEQ ID NO: 8 overlaps each of primers 8, 9, 11, and 13 of Tanaka. Primer 13 provides the 5' end and primer 9 illustrates the 3' end. Further SEQ ID NO: 14 and 15 of the instant application overlaps each or R3, 14 and 15. Finally SEQ ID NO: 9 overlaps 14 10 and 7(12). Thus, guidance to these regions is provided.

Applicant then argues that there is no reasonable expectation of success. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art to select primers which hybridize to the 3' UTR of HCV (col. 2). The prior art disclosed numerous different primer sequences and teaches selection of primers or probes which detect the HCV 3' UTR. The prior art teaches the parameters necessary to vary to achieve specific probes, and the prior art successfully meets this test. This is sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that, In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art fails to identify critical parameters since the prior art provides the parameters necessary for primer selection, including preferred sequence regions (see column 2, lines 48-67 of Tanaka et al), homology considerations (see column 3, lines 11-13), the entire sequence at issue (see Sequence listing), and a variety of particular functional species. Therefore, the prior art provides the information necessary to select probes and primers and the prior art would expect that every species selected in this manner would function in a detection assay. This is also not a situation where only general guidance was given. The prior art provides specific guidance regarding the use of primers and probes from this region of the HCV genome for detection purposes. Therefore, properly applying O'Farrell, it is not simply obvious to try to make the claimed invention, there is a reasonable expectation of success.

The applicant's further argue there is not any such reasonable expectation of success. Applicant's argument directed to there is no reasonable expectation of success is apparently supported by Ausubel. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically

provides "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection. For example, computer programs exist which allow user input for primer selection parameters (see Nucleic Acids Research, 1994). The response asserts that the computers are also not foolproof, however, foolproof is not the standard to be met. As stated in O'Farrell, "obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law non-obvious". Thus, absolute predictability is not required. The art provides the full length sequence of the 3'UTR of HCV, the regions of interest and the approximate size of oligonucleotides to select from this region for detection of the region. Moreover, Tanaka teaches "Any primer which specifically hybridizes the "sequence 3'X" can be used, but those which are highly homologous to the "Sequence 3'X" and have length of about 20 residues are most suitably used". The instant primers and probes are embedded within the nucleic acids of "Sequence 3'X". Thus, SEQ ID NO: ~~1-6~~ 7-9 would be suitable as a primer since it is identical to Sequence 3'X and is of about 20 residues in length. The response asserts that "at best, given what is taught in Tanaka a skilled artisan might only be

motivated to try various probes and primers designed from the 3'-UTR taught in the Tanaka reference". This argument has been reviewed but is not convincing because optimization of primers and primer pairs is routine in the art. The art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claims 14, 16-26, 40-42 above, and further in view of Maertens et al (US Pat. 5,846,704, December 1998).

Neither Tanaka nor Encke specifically teach performing reverse transcriptase with random oligonucleotide primers.

However, Maertens et al teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens

teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the extraction method of Tanaka with the extraction method of Maertens to obtain the claimed invention as a whole. The ordinary artisan would have realized that RNA may be transcribed using either random primers, as taught by Maertens, or primers corresponding to specific HCV RNA, as taught by Tanaka. Since the art teaches that RNA from HCV may be reverse transcribed using either random or specific primers, the ordinary artisan would have realized that they were equivalents and may have substituted random primers for primers corresponding to specific HCV regions.

Response to Arguments

The response traverses the rejection. The response asserts that Maertens does not teach or suggest any of the particular nucleic acid probes and primers of the invention. This argument has been reviewed but is not convincing because as argued above, Taqnaka or Encke both teach the 3' UTR region which is only 98 nucleotides in length, and primer design, absent secondary considerations is obvious. Thus for the reasons above and those already of record, the rejection is maintained.

10. Claims 27-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Maertens et al (US Pat. 5,846,704, December 1998) or Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) as applied to Claims 1, 3-13, 40-42 above, in view of either Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) as applied to Claims 14, 16-26, 40-42 above or Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claims 14, 16-26, 40-42 above.

Maertens et al. teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches primers which have at least 15 contiguous nucleotides from SEQ ID NO: 3 and 4. The inner primers of Maertens denoted as SEQ ID NO: 3 and 4 which overlap at least 15 contiguous nucleotides of the instant SEQ ID NO: 3 and 5/6. Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose gel and ethidium bromide staining (col. 25, lines 14-15)(limitations of Claim 4, 5, 11). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-60)(limitations of Claim 6, 12). As claimed in Maertens Claim 11, the inner primers of the reaction are required to hybridized to SEQ ID NO: 3 and 4. The instant primers of SEQ ID NO: 3, 5 and 6,

would hybridize to SEQ ID NO: 3 and 4 of Maertens in addition to satisfying the teachings that the primers have at least 15 contiguous nucleotides from SEQ ID NO 3 and 4 (limitations of Claim 1, 9-10). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55)(limitations of Claim 43, 45, 54, 56). Thus, Maertens has taught every limitation of the claimed invention.

Neither Maertens nor Han nor Kolykhalov nor Tanaka nor Encke specifically teach a method which combines amplifying both the 5' UTR region and the 3' UTR region for detection of HCV.

However, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Maertens or Han with the teachings of Kolykhalov or Tanaka and Encke to obtain the claimed invention as a whole. The ordinary artisan would have combined the teachings of Maertens or Han with the teachings of Kolykhalov or Tanaka and Encke to generate a more complete and versatile assay for the detection of HCV which encompassed both the 5' UTR region and the 98-base sequence of the 3' UTR region. The art, Han, teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4). The art, Kolykhalov, teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. Additionally, Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV

replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy". The ordinary artisan would have recognized that these two regions were ideal for detecting HCV among numerous isolates. In order to maximize the detection of the number of HCV isolates in a single assay, the skilled artisan would have been motivated to have amplified two regions which were known to detect HCV in a single assay. While the 98-base sequence of the 3' UTR region has demonstrated conservation between isolates of 98-100%, the 3' UTR region of all isolates have not been fully studied. Thus, additionally using conserved regions of the well characterized 5' UTR would have been an additional control which would detect additional isolates which may not have been previously detected using the 98-base sequence of the 3' UTR region. Secondly, the skilled artisan would have also been motivated to have amplified both the 5' and 3' UTR regions of HCV genome simultaneously in a multiplex reaction to detect HCV for the expected benefit of saving time and reagents. The multiplexing of numerous primers into a single reaction has the express benefit of saving reagent by limiting the number of assays and also saving time of scientists since the results may be obtained simultaneously. Therefore, taking two known regions which were ideal for detecting HCV, as taught by the art, and either detecting the two regions separately or in a multiplex reaction would have been obvious to one of ordinary skill in the art such that numerous isolates which may not be detected by one region or one primer pair would be likely detected with the additional regions.

Response to Arguments

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

The response asserts that "at best, given what is taught in Maertens, Han, Kolykhalov, Tanaka and Encke a skilled artisan might only be motivated to try various probes and primers designed from the 5- or 3'-UTR taught in those references". This argument has been reviewed but is not convincing because optimization of primers and primer pairs is routine in the art. The art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target.

Thus for the reasons above and those already of record, the rejection is maintained.

11. Claims 44, 46, 48, 55, 57, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Maertens et al (US Pat. 5,846,704, December 1998) or Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991), in view of either Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) or Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claim 27-39 and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Neither Maertens nor Han nor Kolykhalov nor Tanaka nor Encke specifically teach kit which combines probes and primers from both the 5' UTR region and the 3' UTR region for detection of HCV.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of either Maertens or Han and Kolykhalov or Tanaka nor Encke with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Maertens or Han and Kolykhalov or Tanaka nor Encke into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Maertens or Han and Kolykhalov or Tanaka nor Encke deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers included, into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

12. Claims 1-2, 4-6, 9-12, 43, 45, 54, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maertens et al (US Pat. 5,846,704, December 1998).

Maertens et al (US Pat. 5,846,704, December 8, 1998) teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches primers which have at least 15 contiguous nucleotides from SEQ ID NO: 3 and 4. The inner primers of Maertens denoted as SEQ ID NO: 3 and 4 which overlap at least 15 contiguous nucleotides of the instant SEQ ID NO: 3 and 5/6. Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose

gel and ethidium bromide staining (col. 25, lines 14-15)(limitations of Claim 4, 5, 11). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-60)(limitations of Claim 6, 12). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55)(limitations of Claim 43, 45, 54, 56). Maertens provides specific primers for each of the isolates and universal primers which may be used (Table 4 and 5).

SEQ ID NO: 1 of the instant application overlaps SEQ ID NO: 3 of Maertens. Nucleotides 10-30 of the instant application are identical to nucleotides 1-20 of Maertens.

SEQ ID NO: 2 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 17-25 of the instant application are identical to nucleotides 1-9 of Maertens.

SEQ ID NO: 3 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 5-20 of the instant application are identical to nucleotides 1-15 of Maertens.

SEQ ID NO: 4 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 12-1 of the instant application are identical to nucleotides 1-12 of Maertens.

SEQ ID NO: 5 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 1-21 of the instant application are identical to nucleotides 6-26 of Maertens.

SEQ ID NO: 6 of the instant application contains all 26 of the nucleotides of SEQ ID NO: 4 of Maertens. SEQ ID NO: 6 would be identical except SEQ ID NO: 6 contains an additional A nucleotide on the 3' end of the oligonucleotide.

SEQ ID NO: 7 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 5-25 of the instant application are identical to nucleotides 1-20 of Maertens.

Maertens does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural and functional homologues of the full length disclosed 5' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method and primers of Maertens to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Maertens. The instant primers overlap the primers of Maertens such that it would be presumed that these primers would have the same properties and amplify the same regions. Moreover, any

primers which amplify the 5' UTR region and any probes within the 5' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The rejection is not applicable to the primer pair of SEQ ID NO: 1 and 4 and the primer pair of SEQ ID NO: 2 and 7, since the specification provides unexpected results with respect to these primer pairs.

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. Applicants cite *In re Deuel, In re O'Farrell* and states that there is no reasonable expectation of success.

Applicant's cite a passage, in addition to the passage provided, in *Deuel* which is deemed to support applicant's position. The examiner agrees with the position that the Deuel court states "in all of these cases...the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention". However, the examiner also notes that Deuel teaches at 1215, col. 1, No. 7, "Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules". In contrast, in the instant case, the very source of the claimed nucleic acid was provided.

The reference even directs the attention to the very region the oligonucleotides are pulled from. Deuel did not find it obvious to probe a library to find full length DNA molecules given a smaller portion of the molecule. The instant case, however, is directed to a known full length molecule and determining smaller molecules which may function as probes and/or primers. Thus, the normal circumstances for a prima facie case should be followed as set out on 1214, col. 2.

Applicant then argues that there is no reasonable expectation of success. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art to select primers which hybridize to the 5' UTR of HCV for detection of the nucleic acid. Further, since the art teaches the SEQ ID NO: 3, 5-7, 13-14, 16 and a nucleic acid comprising SEQ ID NO: 4, the art has provided specific motivation and teachings to choose the probes and primers for the HIV-1 and HIV-2 detection. These probes and primers were used in a multiplex analysis of HIV-1 and HIV-2 detection, thus there is motivation to select these sequences for multiplex analysis. With respect to choosing primers for 5' HCV detection, the prior art disclosed numerous different primer sequences and teaches selection of primers or probes which detect the HCV 5' UTR. The prior art teaches the parameters (i.e. size, parameters, homology) necessary to vary to achieve specific probes, and the prior art successfully meets this test. This is

sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that, In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. For the 5' UTR primers, this is not a situation where the prior art fails to identify critical parameters since the prior art provides the parameters necessary for primer selection, including preferred sequence regions, the entire sequence at issue, and a variety of particular functional species. Therefore, the prior art provides the information necessary to select probes and primers and the prior art would expect that every species selected in this manner would function in a detection assay. This is also not a situation where only general guidance was given. The prior art provides specific guidance regarding the use of primers and probes from this region of the HCV genome for detection purposes. Therefore, properly applying O'Farrell, it is not simply obvious to try to make the claimed invention, there is a reasonable expectation of success.

The applicant's further argue there is not any such reasonable expectation of success. Applicant's argument directed to there is no reasonable expectation of success is apparently supported by Ausubel. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that

is lea[illegible]edictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection. For example, computer programs exist which allow user input for primer selection parameters (see Nucleic Acids Research, 1994). The response asserts that the computers are also not foolproof, however, foolproof is not the standard to be met. As stated in O'Farrell, "obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law non-obvious". Thus, absolute predictability is not required. The art provides the full length sequence of the 5'UTR of HCV, the regions of interest and the approximate size of oligonucleotides to select from this region for detection of the region. Further, optimization of primers and primer pairs is routine in the art. The art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target. As noted in *In re Aller*, 105 USPQ 233 at

235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Allowable Subject Matter

13. In the specification Applicants have provided comparison results for the 5' NCR primers of the present invention and the Roche assay. Applicants have compared the primer pair SEQ ID NO: 1, 4 and SEQ ID NO: 2,7 with the Roche primers. It is noted that applicants have not provided the exact Roche primers which were compared. Applicants have shown that the instant primer pairs detect more positive results than the Roche primers. Since it is presumed that the positive results detected were samples which were infact infected, the instant primer pairs (SEQ ID NO: 1 and 4 and SEQ ID NO: 2 and 7), have unexpected results and are not obvious over the prior art. Applicants have compared their invention to the prior art and shown that improved results were found for the specific primer pairs. It is noted that applicants have not showed unexpected results for the individual primers, only the primer pairs.

Conclusion

14. No claims allowable over the art.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
October 12, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600